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EXAMINER	
GAMBEL, P	
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DATE MAILED: 07/25/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☑ Responsive to communication filed on 103 10/31/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-9 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 1-9 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

15. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The title should be directed to the use of C5-specific antibodies as this is the key feature of the claimed invention.

16. Formal photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

Photographs are not acceptable until petition is granted as set forth in 37 CFR 1.84(b). Under 37 CFR 1.84(b), the applicant must file a petition with fee requesting acceptance of the black and white photographs. The petition is decided in the Office of the Group Director.

17. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. The specification is objected to and claims 1-9 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

Applicant has not disclosed how to use C5-specific antibodies to treat glomerulonephritis by reducing the cell-lysing ability of complement present in the patient's blood with C5/C5b-specific antibodies. A C5-specific antibody was able to diminish complement-mediated activation during extracorporeal treatment only (see examples 1-4). There is insufficient evidence or nexus with respect to the in vivo operability of C5-specific antibodies to use applicant's invention for the reasons

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs such as antibodies can be species- and model-dependent, it is not clear that reliance on the disclosed working examples accurately reflects the efficacy of the claimed methods. Applicant has disclosed the prevention of the generation of C5b-9 during extracorporeal circulation wherein the anti-C5 antibodies were added at or near

the time of CPB initiation (Example 3) or on various aspects of platelet-leukocyte activation (Example 4) the prevention of platelet/leukocyte activation and adhesion during extracorporeal circulation addition of the C5-specific antibody the initiation of CPB circuit circulated through an extracorporeal circuit.

The specification does not adequately teach how to effectively inhibit the disease/treatment endpoint in humans by administering an inhibiting monoclonal antibody. The specification does not teach how to extrapolate data obtained from these controlled conditions evaluating extracorporeal treatment with C5/C5b-specific antibodies to the development of effective in vivo human therapeutic methods which are directed toward a chronic ongoing disease. Also, it is not clear whether the administration of C5/C5b-specific antibodies would be neutralized by the patient's complement found in the circulation. Also, therapy relying on antibodies and complement inhibitors have not been successful as set forth presently.

Pharmaceutical therapies are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Concerning antibody therapy, Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3)(Tibtech, 1993). However, it is well known in the art that the clinical efficacy of antibody therapy including humanized antibodies have been limited by specificity, binding constants, tissue penetration, clearance rates and the mode of action of the effector are presented. Therefore, the art indicates that even humanized antibodies are not necessarily predictable in their efficacy. For example, Mountain et al. teach that most antibody-based therapies are very unlikely to achieve success with a single dose (Biotechnology and Genetic Engineering Reviews, 10: page 11, paragraph 1, first sentence, 1993). Murine antibodies are limited to one or perhaps two doses and the administration of further doses leads to accelerated clearance and in many cases to complete abrogation of efficacy

(Mountain et al., pages 10-11, overlapping paragraph). Therefore, the success of multiple dosing as indicated in the claimed therapeutic regimen would not be predictive.

Concerning therapeutic complement inhibitors, Liszewski et al. state that there are no inhibitors of complement activation utilized in clinical medicine (see page 932, column 1, paragraph 1; Paul, Fundamental Immunology, 1993). The procedures used for the characterization of protein therapeutics has not been cut-and-dried and that the extent of characterization necessary appears to be decided on a case-by-case basis.

In a review of clinical complementology, Morgan discloses that the use of biological agents offer potential therapeutics, there is still no pharmacological agents which provide a safe, effective means of inhibiting complement activation (Eur. J. Clin. Invest., 1994; see entire document, page 224, column 2, Complement inhibitors in therapy). In disclosing the effectiveness of the soluble CR1 inhibitor, it is noted that other potential regulators subject to research interest had yet proved an effective inhibitors as soluble CR1 in vivo or in vitro (page 225, column 1, paragraph 2). Also, the treatment of chronic conditions would require inhibition of complement over long periods of time which could prove difficult and could leave the recipient susceptible to infections (page 225, column 1, paragraph 3).

Similarly, Kalli et al. reviews the potential therapeutic uses of recombinant complement protein inhibitors (Springer Semin. Immunopathol., 1994). Here, several requirements must be met in order for a complement inhibitor to be clinically useful (page 421, paragraph 2). A complement inhibitor (1) should inhibit both the alternative and classical pathways of complement activation, (2) should have a high affinity for the multivalent complexes of C3b and C4b found in the convertases, (3) should irreversibly inactivate the convertases and (4) should be able to recycle and inhibit multiple convertases.

Applicant is reminded of the factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Therefore, in view of the lack of predictability of the art to which the invention pertains, the lack of established clinical protocols for effective antibody/complement inhibitor-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting the cell-lysing ability of complement in the treatment of glomerulonephritis.

19. Claim 1-8 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-8 are indefinite in the recitation an antibody that "binds to" and an antibody "to" because "specifically binds" would be appropriate in defining the intended specificity of the C5-specific antibodies.

B) Claims 6-9 are indefinite in the recitation of "pharmaceutical agent" because it is unclear whether applicant is claiming a compound or composition. The claim reads on a compound per se. If applicant wants to claim a pharmaceutical composition, then the C5-specific antibody should be claimed with a pharmaceutically acceptable carrier, minimally. Specific activity and dosages can be claimed as well. If applicant wants to claim the C5-specific antibody as a compound, then the term comprises should not be used.

C) Claims 7-9 should be deleted since they are essentially a duplicative of claim 7. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

The amendments must be supported by the specification so as not to add any new matter.

20. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

21. Claims 1-5 are rejected under 35 U.S.C. § 103 as being unpatentable over Wurzner et al. (Complement Inflamm., 1991; # 20) in view Couser et al. (J. Am. Soc. Nephrol., 1991; 1449, #5) and Sims et al. (U.S. Patent No. 5,135,916; 1449, #1). Claims 1-5 are drawn to the use of C5/C5b-specific antibodies to inhibit complement in the treatment of glomerulonephritis.

Wurzner et al. teach the claimed C5-specific antibodies, as disclosed in example 1 of the specification (see entire document). These C5-specific antibodies exhibited strong inhibitory activities with respect to terminal complement complex generation, C5a generation and complement-mediated hemolysis (see Results, particularly pages 334-335). It is noted that the anti-C5-specific antibodies exhibited stronger inhibitory activity than C6-specific antibodies in hemolysis assays (see page 336, column 2). Wurzner et al. clearly teaches the application of C5 (and C6) depletion in various diseases including glomerulonephritis and nephritis (Discussion, particularly, page 337). Wurzner et al. concludes that the biological consequences of C5a and terminal complement complex generation can be circumvented by these monoclonal antibodies (see Discussion). The instant antibodies taught by Wurzner et al. were employed in a number of immunological assays, which would have required the use of standard buffers (see Materials and Methods) and their storage. Such buffers as PBS were well known in the art for the storage and use of antibodies. Also, the reference teaches the use of these antibodies in analyzing the specific regions on C5 and C6 which are involved in complement complex formation (see Discussion, final paragraph).

Couser et al. references teach the role of complement including the role of C5b-9 in mediating glomerulonephritis (see entire document). Couser et al. (JASN, 1991) teach that C6 depletion studies including the use of antibodies to deplete C6 could ameliorate the deleterious effects of complement deposition and activation (Introduction). In the Discussion, it is taught that the mechanism of action by which C6 works is through C5b-9 (page 898, for example).

It was art-known at the time the invention was made that C5b-9 is a complex that results from proteolytic cleavage of C5 to generate C5b which then combines with C6 and C7 to form

Cb5,6,7.

As a general teaching reference, Sims et al. teach making C5b-9 specific inhibitors antibodies for inhibiting complement activation associated with autoimmune disorders (see entire document including Summary of the Invention and column 3, lines 20-23. This reference teaches the storage and in vitro and in vivo use of C5b-9 inhibitors.

Therefore, the ordinary artisan was motivated at the time the invention was made to make C5b-9 inhibitors as a means to treat complement-mediated pathology associated with glomerulonephritis, as taught by the references above. Wurzner et al. teach that the instant antibodies had features such as inhibitory activities with respect to terminal complement complex generation, C5a generation and complement-mediated hemolysis, that were particularly attractive as therapeutic agents to block complement-mediated effects in vivo. In addition, Wurzner et al. teach that these features of the instant antibodies had advantages over C6-specific antibodies that also operate as C5b-9 inhibitors, as taught by Wurzner et al. and Crouser et al. Since C6-specific antibodies exemplify in vivo inhibitory effects as taught by Couser; the ordinary artisan would have had motivation to apply the instant C5-specific antibodies in the same or similar treatment methods of ameliorating nephritis.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to apply C5/C5b-specific antibodies as complement inhibitors in the treatment of glomerulonephritis. From the teachings of the reference, it was apparent one of ordinary skill in the would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention was a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

22. Claims 6-9 are rejected under 35 U.S.C. § 103 as being unpatentable over Wurzner et al. (Complement Inflamm., 1991; 1449, #20). Claims 6-9 are drawn to articles of manufacture comprising packaging material and C5-specific antibodies.

Wurzner et al. teach the instant C5-specific antibodies, as disclosed in the specification. Wurzner et al. employed these C5-specific antibodies in a number of immunological assays, which would have required the use of standard buffers (see Materials and Methods) and their storage. Such buffers as PBS were well known in the art for the storage and use of antibodies. Also, the reference teaches the use of these antibodies in analyzing the specific regions on C5 and C6 which are involved in

complement complex formation (see Discussion, final paragraph).

This reference differs from the claimed article of manufacture (e.g. a kit) by not indicating packing material and labels per se. It was a well known convention in the art to place antibodies with packing material and labels for convenience and economy, whether it was being used in the lab where they were made or was sent off to another lab for evaluation. Therefore, the article of manufacture comprising C5-specific antibodies taught by the reference appears to be either identical with or only slightly different from the instant claims.

Applicant is reminded that a composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982). Therefore, the intended use and dosages do not change the claimed article manufacture of C5-specific antibodies from being C5-specific antibodies. Applicant is reminded that claims 7-9 were rejected under 35 U.S.C. § 112, second paragraph, for being duplicative of independent claim 6 and not further limiting the independent claim (see section 19 above).

Therefore,one of ordinary skill in the art at the time the invention was made would have been motivated to apply C5-specific antibodies as C5b-9 inhibitors and to put these inhibitors in a convenient article of manufacture to inhibit complement activation in for various in vitro and in vivo applications procedures. From the teachings of the reference, it was apparent one of ordinary skill in the would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention was a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

23. No claim is allowed.

24. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Margaret Parr can be reached on (703) 308-2454. The fax phone number for Group 180 is (703) 305-3014 or (703) 308-4227. The fax phone number for Art Unit 1806 is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
July 24, 1995